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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,029	MILLAR, DOUGLAS SPENCER	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-30* is/are pending in the application.

4a) Of the above claim(s) *20-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-19 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed August 11, 2009 is acknowledged. Claims 1, 4, 5, 7 and 8 (currently amended), claims 6, 9-19 and 30 (original or previously presented) and claim 30 (newly added) will be examined on the merits. Claims 2 and 3 are newly canceled and claims 20-29 were previously withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 4-19 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Step (b) of amended base claim 1 provides two populations of primers while step (c) includes the limitations of contacting the modified DNA of step (a) with nucleotides and a polymerase capable of amplifying double stranded DNA. However, it is unclear how amplification can occur without also including the primers of step (b) in the amplification step (c).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 4, 5, 8-13 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dean et al. (Proc. Natl. Acad. Sci. U.S.A. (2002) 99:5261-5266, submitted on IDS) in view of Berlin, K. (U.S. Patent No. 7,008,770) and further in view of Olek (Nucleic Acids Res. 24:5064-5066, submitted on IDS) and further in view of Raizis et al. (Anal. Biochem. 226:161-166, submitted on IDS).

With regard to claims 1, 3, 4, 8, 9 and 30, Dean teaches a method for whole genome amplification (WGA) (for overview, see Abstract and p. 5261, column 1, second paragraph) comprising:

(b) providing a population of random X-mers of exonuclease-resistant primers capable of binding to at least one strand of the modified DNA, wherein X is an integer 3 or greater (exonuclease-resistant hexamers containing thiophosphate were provided, p. 5261, column 2, lines 10-11 and 33-34);

(c) contacting the modified DNA with nucleotides and a polymerase capable of amplifying double stranded DNA (a reaction mix was prepared containing human genomic DNA, dNTPs, hexamer primers and phi29 DNA polymerase, p. 5261, column 2, lines 30-37); and

(d) allowing the polymerase to amplify the modified DNA (multiple displacement amplification, MDA, occurred during incubation at 30^0C for 18 hr, p. 5261, column 2, lines 37-38, p. 5263, column 1, lines 4-11 and Figure 1; the genomic DNA is not substantially degraded since there is no high temperature denaturation step used, p. 5263, column 2, lines 29-43).

With regard to claim 5, Dean teaches a method wherein the exonuclease-resistant primers are oligonucleotides or oligonucleotide analogues containing at least one intercalator pseudonucleotide forming an intercalating nucleic acid (INA) (hexamers are phosphorothioate-containing oligonucleotides, p. 5261, column 2, lines 10-11 and 33-34).

With regard to claims 10 and 11, Dean teaches a method wherein the primers contain from 3 to 40 bases, or about 6 to 20 bases (exonuclease-resistant hexamers containing thiophosphate were provided, p. 5261, column 2, lines 10-11 and 33-34).

With regard to claims 12 and 13, Dean teaches a method wherein the polymerase is selected from phi29, or a modified version thereof, or a functional equivalent thereof capable of amplifying double stranded DNA in vitro without the need to denature the DNA (phi29 DNA polymerase is used in MDA reactions, p. 5261, column 2, lines 30-37, thus avoiding the need for denaturation of the genomic DNA template, p. 5263, column 2, lines 29-43).

Dean does not teach a method wherein genomic DNA is treated with a modifying agent which modifies cytosine bases but does not modify 5'-methyl-cytosine bases under conditions to form single stranded modified DNA, and wherein the agent is bisulphite, acetate or citrate, including sodium bisulphite. Dean does not teach a method wherein the primers are formed of two populations of INA primers comprising random X-mers containing either the bases A, G and T or the bases A, C and T, wherein one population of primers is capable of binding to one strand of DNA while the

other population of primers is capable of binding to a complimentary synthesized strand of the DNA stand to which the first population of primers bind.

Berlin teaches a method for performing complex PCR amplifications such as whole genome amplifications (column 1, lines 7-12) wherein the template DNA is first treated with a reagent such as bisulphite that reacts differently with 5-methylcytosine and cytosine to change their base-pairing behavior (column 4, lines 37-44). Berlin also teaches a method wherein two populations of primers are used, one containing bases A, G and T and the other containing bases A, C and T, wherein one population binds to one strand while the other binds to the complementary strand and wherein at least on population can contain degenerate base positions (column 4, lines 33-35, column 5, lines 4-14 and column 6, lines 46-58). Berlin also teaches that the whole genome amplification method of bisulphite-treated genomic DNA can be used for the investigation of cytosine methylation patterns in the DNA sample (column 6, lines 6-17).

Olek teaches an improved method for modification of DNA with sodium bisulphite for analysis of cytosine methylation in which the bisulphite treatment is performed on material embedded in agarose beads, resulting in formation of single-stranded modified DNA in the agarose since the denatured strands are prevented from renaturing in the agarose during chemical treatment (see Abstract and p. 5064, column 1, last line to column 2, line 5).

Raizis teaches a method for bisulphite treatment of DNA that minimizes template degradation, including reduction of the time required to achieve completion of the

bisulphite reaction using higher concentrations of bisulphite (p. 162, column 1, line 21 to column 2, line 34 and p. 165, column 2, line 15 to p. 166, column 1, line 5).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the whole genome amplification (WGA) methods of Dean and Berlin using nuclease-resistant hexamer primers to amplify genomic DNA by multiple displacement amplification (Dean) and amplifying bisulphite-treated DNA using primers containing 3 of 4 bases (Berlin) with the methods of Olek, who teaches sodium bisulphate treatment of DNA embedded in agarose to form and maintain the DNA in single-stranded form during treatment, since the methods of bisulphite treatment of Berlin and Olek can be easily adapted to the WGA methods of Dean with appropriately designed primers to amplify bisulphite-modified templates. Furthermore, the whole genome methods of Dean and Berlin can easily be combined with the bisulphite treatment methods of Raizis that minimizes template degradation since the methods of bisulphite treatment of Raizis can be easily adapted to the WGA methods of Dean and Berlin and the agarose-based method of bisulfite treatment of Olek with appropriately designed primers to amplify non-degraded bisulphite-modified templates. Thus, an ordinary practitioner would have been motivated to combine the methods of Dean, Berlin, Olek and Raizis since the hexamer primers taught by Dean can be designed to contain appropriate base compositions to amplify both the bisulphite-modified template and PCR products complementary to the original template. The bisulphite method of Berlin for performing WGA has the advantage by allowing identification of targets strands containing 5-methylcytosone versus cytosine bases by

using primers which bind to the treated strand or the complement of the treated strand (Berlin, column 2, lines 39-49, column 3, lines 37-43 and column 4, line 61 to column 5, line 14). Furthermore, the agarose-based methods of Olek increase sensitivity of detection by providing complete bisulphite treatment of the single-stranded template and also minimize loss of material by eliminating DNA isolation or precipitation steps (Olek, p. 5064, column 1, last line to column 2, line 5 and p. 5065, column 2, line 12 to p. 5066, column 2, line 4). Moreover, Berlin indicates that one preferred method of bisulphite treatment for preparation of DNA for PCR and methylation analysis is the agarose method of Olek (Berlin, column 9, lines 14-26). Furthermore, the methods of Raizis avoid excessive depurination that causes fragmentation and reduction of full-length template molecules, and thus avoiding such fragmentation dramatically increases the sensitivity of detection of modified target sequences (Raizis, p. 161, column 2, lines 18-25 and p. 165, column 2, line 15 to p. 166, column 1, line 5). This method can be easily adapted to the bisulphite methods of Berlin and Olek for efficient preparation of samples for WGA.

6. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dean et al. (Proc. Natl. Acad. Sci. U.S.A. (2002) 99:5261-5266, submitted on IDS) in view of Berlin, K. (U.S. Patent No. 7,008,770) and further in view of Olek (Nucleic Acids Res. 24:5064-5066) and further in view of Raizis et al. (Anal. Biochem. 226:161-166) as applied to claims 1, 4, 5, 8-13 and 30 above, and further in view of Christensen et al. (U.S. Patent Pub. No. 2006/0014144).

Dean, Berlin, Olek and Raizis together teach the limitations of claims 1, 4, 5, 8-13 and 30, as discussed above. However, neither Dean, Berlin, Olek nor Raizis teach a method wherein the oligonucleotide or oligonucleotide analogues used as exonuclease-resistant primers are intercalating nucleic acids (INAs) and selected from the group consisting of subunits of DNA, RNA, peptide nucleic acid (PNA), hexitol nucleic acid (HNA), MNA, altritol nucleic acid (ANA), locked nucleic acid (LNA), cyclohexanyl nucleic acid (CAN), CeNA, TNA, (2'-NH)-TNA, nucleic acid based conjugates, (3'-NH)-TNA, α -L-Ribo-LNA, α-L-Xylo-LNA, β-D-Xylo-LNA, α-D- Ribo-LNA, [3.2.1]-LNA, Bicyclo-DNA, 6-Amino-Bicyclo-DNA, 5-epi-Bicyclo-DNA, α-Bicyclo-DNA, Tricyclo-DNA, Bicyclo[4.3.0]-DNA, Bicyclo[3.2.1]-DNA, Bicyclo[4.3.0]amide-DNA, β-D-Ribopyranosyl-NA, α-L-Lyxopyranosyl-NA, 2'-R-RNA, 2'- OR-RNA, α-L-RNA, and β-D-RNA.

Christensen teaches an oligonucleotide or oligonucleotide analogues comprising at least one intercalator pseudonucleotide (paragraph 24, lines 1-3) that increase nuclease stability of the oligonucleotide (paragraph 30), and include analogues such as PNA, HNA, MNA, ANA, LNA, TNA and others (paragraph 167, lines 1-23).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the whole genome amplification (WGA) methods of Dean, Berlin, Olek and Raizis using nuclease-resistant hexamer primers to amplify genomic DNA by multiple displacement amplification (Dean) and amplifying bisulphite-treated DNA using primers containing 3 of 4 bases (Berlin) after bisulphite treatment by the methods of Olek and Raizis with the teachings of Christensen for oligonucleotides containing intercalator analogues such as PNA, HNA, MNA, ANA,

LNA, TNA, since these analogues can be easily substituted in the exonuclease-resistant primers taught in the WGA methods of Dean using templates prepared by the bisulphite methods of Olek and Raizis. Thus, an ordinary practitioner would have been motivated to combine the methods of Dean, Berlin, Olek and Raizis with the teachings of Christensen since the intercalator analogues of Christensen (paragraph 167, lines 1-23), which also include phosphorothioates as also practiced by Dean for designing exonuclease-resistant primers (Dean, p. 5261, column 2, lines 10-11 and 33-34), not only can intercalate into a double helix at a predetermined position, but also increase the affinity of such oligonucleotides for DNA, substantially increase the specificity of hybridization, reduce cross- and self-hybridization and increase nuclease stability of the oligonucleotide (Christensen, paragraphs 25-30), all parameters that would be useful in whole genome amplification of a template nucleic acid.

7. Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dean et al. (Proc. Natl. Acad. Sci. U.S.A. (2002) 99:5261-5266, submitted on IDS) in view of Berlin, K. (U.S. Patent No. 7,008,770) and further in view of Olek (Nucleic Acids Res. 24:5064-5066, submitted on IDS) further in view of Raizis et al. (Anal. Biochem. 226:161-166) as applied to claims 1, 4, 5, 8-13 and 30 above, and further in view of Hogrefe et al. (U.S. Patent Pub. No. 2003/0143577).

Dean, Berlin, Olek and Raizis together teach the limitations of claims 1, 4, 5, 8-13 and 30, as discussed above. However, neither Dean, Berlin, Olek nor Raizis teach a method for WGA wherein the polymerase comprises a polymerase cocktail comprising

a mixture of at least one proof-reading DNA polymerase selected from the group consisting of Pfu polymerase, Pfu polymerase turbo, Vent polymerase, Vent exo-polymerase, Pwo polymerase, 9°NmDNA polymerase, Therminator, Pfx DNA polymerase, Expand DNA polymerase, rTth DNA polymerase, and DyNAzyme EXT Polymerase and at least one non proof-reading DNA polymerase selected from the group consisting of Taq polymerase, Taq polymerase Stoffel fragment, Advantage DNA polymerase, AmpliTaq, Amplitaq Gold, Titanium Taq polymerase, KlenTaq DNA polymerase, Platinum Taq polymerase, and Accuprime Taq polymerase, wherein the ratio of proof-reading polymerase to non proof-reading polymerase is at least about 1:2-1:10 and wherein amplification is carried out by DNA thermal cycling.

Hogrefe teaches high fidelity DNA polymerase compositions comprising a wild-type non-proofreading DNA polymerase such as Taq DNA polymerase and a mutant DNA polymerase such as Pfu DNA polymerase with full 3' to 5' exonuclease activity but about 90% or more reduced DNA polymerization activity relative to wild-type activity (paragraph 12, lines 1-6 and paragraph 75, lines 1-7), wherein the polymerase composition can be used in PCR reactions requiring thermal cycling (paragraph 223, lines 1-4).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the whole genome amplification (WGA) methods of Dean, Berlin, Olek and Raizis using nuclease-resistant hexamer primers to amplify genomic DNA by multiple displacement amplification (Dean) and amplifying bisulphite-treated DNA using primers containing 3 of 4 bases (Berlin) after bisulphite

treatment by the methods of Olek and Raizis with the teachings of Hogrefe for amplification of DNA using DNA polymerase cocktails of both proof-reading and non-proof-reading polymerases since such cocktails provide both high polymerization activity and high levels of polymerization fidelity and are easily substituted in the WGA assays of Dean, Berlin, Olek and Raizis. Thus, an ordinary practitioner would have been motivated to combine the methods of Dean, Berlin, Olek and Raizis with the high fidelity DNA polymerase compositions taught by Hogrefe since Hogrefe provides a polymerizing system that achieves both high fidelity without compromising product yield needed for WGA since the proof-reading polymerase is modified to reduce polymerization and thus does not compete with the highly processive non-proof-reading enzyme (Hogrefe, paragraph 8, lines 1-11 and paragraph 66, lines 1-13). Hogrefe teaches that such high-fidelity polymerase blends are useful in a variety of applications requiring PCR (see paragraph 311), and thus would be highly suitable for applications such as WGA using modified primers and bisulphate-modified templates.

Response to Arguments

8. Applicant's arguments filed August 11, 2009 have been fully considered but they are not persuasive.

Applicant then argues that the 35 USC § 103(a) rejection of claims 1, 3-5 and 8-13 over Dean et al. (Proc. Natl. Acad. Sci. U.S.A. (2002) 99:5261-5266) in view of Berlin, K. (U.S. Patent No. 7,008,770) and further in view of Olek (Nucleic Acids Res. 24:5064-5066) should be withdrawn based on the following arguments. Applicant

argues that, based on the Declaration provided by the inventor, Dr. Douglas Spencer Millar, the method allows amplification of bisulphite, acetate or citrate-treated genomic DNA without substantial fragmentation to generate long amplification products and that this method provides significant advantages over methods disclosed by the cited prior art. In particular, Applicant argues that the whole genome amplification method of Dean does not distinguish between methylated and non-methylated cytosines and therefore cannot be used for methylation analysis. Applicant argues that the method of Olek teaches fragmentation of genomic DNA prior to bisulphite treatment and therefore the amplification products are considerably smaller than those obtained by the claimed method using non-fragmented DNA. Applicant then argues that using the method of Berlin for whole genome amplification using at least 50 primers directed to one strand would also result in relatively small amplification products. Applicant further argues that the method of Raizis, while teaching a method for bisulphite treatment of DNA that minimizes template degradation, is used for treatment and amplification of large numbers of copies of plasmid DNA, in contrast to the claimed invention where as little as 10 copies of genomic DNA is treated without substantial degradation to obtain amplification products greater than 20 kb in length. In summary, Applicant argues that the claimed invention provides unexpected results not obtainable by the combination of the methods of the cited art.

The Examiner asserts that the claims are not directed to obtaining a specific result other than amplified DNA after treatment of the sample with agents that specifically modify methylated cytosine bases. The size range of the amplified DNA is

not included as a limitation, whereas the arguments made in the Declaration are directed at obtaining the unexpected result of products greater than 20 kb in length. The only reference to size in claim 1 cites that the modifying treatment does not result in substantial DNA fragmentation of the starting DNA prior to amplification. Without a precise definition in the specification of what is meant by the term "substantial", it is not possible to directly compare the results of bisulphite treatment methods of the cited art with the claimed methods with regard to fragmentation. However, a comparison of the conditions for treatment is possible. Olek teaches treatment of DNA in agarose beads by incubating the sample in 5 M bisulphite solution for four hours at 50°C (p. 5065, column 1, lines 6-11), while Berlin teaches treatment of genomic DNA in solution using the conditions of Olek (column 7, lines 33-35). Raizis also teaches similar treatment of DNA in solution by incubating the sample in 5 M bisulphite solution for four hours at 50°C (p. 162, column 1, line 21 to column 2, line 19) and compared this treatment with overnight treatment using 3.1 M. bisulphite and noted relatively little DNA fragmentation by comparison (p. 164, column 1, lines 1-16). The methods of the current invention include incubation of the sample in 2M bisulphite solution overnight at 55°C (p. 11 of specification, lines 15-19). While Applicant argues that Raizis only tests amplification of plasmid DNA after bisulphite treatment, it is clear that the preferred treatment conditions of Raizis for genomic DNA result in much longer fragments compared to overnight treatment with 3 M bisulphite at 50°C (p. 164, column 1, lines 6-11 and lanes 2 and 3 in Figure 4), which is similar to the treatment cited in the current invention. Thus, one of ordinary skill in the art would recognize that the methods for cytosine modification

taught by Olek, Berlin and particularly Raizis that result in relatively little DNA fragmentation would be useful for pretreatment of DNA prior to applying methods for whole genome amplification, such as taught by Dean and Berlin. Though methods such as Olek may, in addition, teach fragmentation by restriction enzyme digestion, this represents a completely different step from bisulphite treatment, which may itself result in fragmentation. The inclusion of a step such as restriction enzyme treatment is not inconsistent with the steps of instant claim 1, which only require that the treatment step that modifies cytosine bases not result in "substantial" fragmentation. Therefore, all of the limitations of the claims are taught or suggested by the prior art and the 103(a) rejection of claims 1, 4, 5, 8-13 and 30 over Dean in view of Berlin and further in view of Olek and Raizis is maintained.

Applicant further argues that the 103(a) rejection of claims 6 and 7 over Dean, Berlin, Olek and Raizis and further in view of Christensen and the 103(a) rejection of claims 14-19 over Dean, Berlin, Olek and Raizis and further in view of Hogrefe should be withdrawn since neither of these references teach or suggest reduction in substantial DNA fragmentation as required by the base claim. Since the rejection of these claims over Christensen or Hogrefe is not further argued beyond what is discussed above, the rejections are maintained.

Summary

9. Claims 1, 4-19 and 30 are rejected. No claims are allowable.

Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637